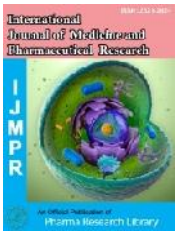
International Journal of Medicine and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijmpr



Review Article **Open Access**

Recent Advances in the Treatment of Diabetic Foot

Subramanyam Kumuda*, Saritha Chandra, Dr. P. Venkatesh

Jagan's College of Pharmacy, Jangala Kandriga (V), Muthukur (M), SPSR Nellore-524348.

A B S T R A C T

Diabetic foot is a very serious complication of diabetes and is defined as a foot affected by ulceration associated with diabetic neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. The prevalence of diabetic foot in diabetic population is 4-10% and condition is more frequent in older patients. Recent advances in the treatment of diabetic foot include the use of Becaplermin gel which is a platelet derived growth factor (PDGF) of recombinant human origin. PDGF stimulates angiogenesis, wound contraction and wound remodeling. Living skin equivalent (LSE) products are newest technological advances for diabetic foot ulcers. One LSE product consists of dermal fibroblasts cultured in vitro and has histological characters similar to dermal papillary of newborn skin. Extracellular Matrix Proteins are semi synthetic ester of hyaluronic acid which facilitates the growth and movement of fibroblasts and controls hydration.MMP Modulators contains matrix metallo proteinases which regulate the extracellular matrix components. Negative Pressure Wound Therapy involves the use of continuous sub-atmospheric pressure through a special pump covered with adhesive drape to maintain a closed environment, Hyperbaric Oxygen accelerates wound healing in diabetes. Foot problems in a person with diabetes can have disastrous consequences. Though recent advances in the management of these problems have increased the abilities to save the lower limb, the best management remains the control of diabetes and prevention of diabetic foot.

Keywords: Diabetic foot, ulcers, amputation

A R T I C L E I N F O

CONTENTS

Article History: Received 19 August 2016, **Accepted** 24 September 2016, **Available Online** 10 October 2016

***Corresponding Author**
Subramanyam Kumuda
Jagan's College of Pharmacy,
Jangala Kandriga, Nellore-524348.
Manuscript ID: IJMPR3158

PAPER-QR CODE

Citation Subramanyam Kumuda, *et al.* Recent Advances in the Treatment of Diabetic Foot. *Int. J. Med. Pharm. Res.*, 2016, 4(5): 305-311.

1. Introduction

Diabetic foot is one of the most significant and devastating complications of diabetes. It is estimated that about 5% of all patients with diabetes present with a history of foot ulceration, while the lifetime risk of diabetic patients developing this complication is 15% [1-2]. The majority of foot ulcers heal, while some of them remain active, and 5-24% of them finally lead to limb amputation. Neuropathic wounds are more likely to heal over a period of 20 weeks, while neuro ischemic ulcers take longer and more often lead to limb amputation. It has been found that 40-70% of all non traumatic amputations of the lower limbs occur in patients with diabetes. Furthermore, many studies have reported that foot ulcers precede approximately 85% of all amputations performed in diabetic patients [3-4] The risk of foot ulceration and limb amputation increases with age and the duration of diabetes. The prevention of diabetic foot is crucial, considering the negative impact on a patient's quality of economic burden on the healthcare system [5].Diabetic foot ulceration is a major health problem and its management involves a multidisciplinary approach [6].

Objectives

To describe the pathogenesis, causes, symptoms and diagnosis of diabetic foot. To highlight the recent advances in the treatment of diabetic foot, so that the amputations related to diabetes is reduced.

2. Pathogenesis

The most significant risk factors for foot ulceration are diabetic neuropathy, peripheral arterial disease, and consequent traumas of the foot. Diabetic neuropathy is the common factor in almost 90% of diabetic foot ulcers. Nerve damage in diabetes affects the motor, sensory, and autonomic fibers. Motor neuropathy causes muscle weakness, life atrophy and paresis. The Sensory neuropathy associated leads to loss of the protective sensation of pain, pressure, and heat. Autonomic dysfunction causes vasodilatation and decreased sweating resulting in a loss of skin integrity, providing a site vulnerable to microbial infection [7-8] Peripheral arterial disease is 2-8 times more common in patients with diabetes, starting at an earlier age, progressing more rapidly, and usually being more severe than in the general population. It commonly affects the segments between the knee and the ankle. It has been proven to be an independent risk factor for cardiovascular disease as well as a predictor of the outcome of foot ulceration. Even minor injuries, especially when complicated by infection, increase the demand for blood in the foot, and an inadequate blood supply may result in foot ulceration, potentially leading to limb amputation. The majority of foot ulcers are of mixed etiology (neuro ischemic), particularly in older patients [9] Other risk factors for foot ulceration include a previous history of foot ulceration or amputation, visual impairment, diabetic nephropathy, poor glycemic control, and cigarette smoking. Some studies have shown that foot ulceration is more common in men with diabetes than in women. Social factors, such as low socioeconomic status, poor access to healthcare services, and poor education are also proven to be related to more frequent foot ulceration [4][10].

3. Causes of Diabetic Foot

Footwear: Poorly fitting shoes are a common cause of diabetic foot problems. If the patient has red spots, sore spots, blisters, corns, calluses, or consistent pain associated with wearing shoes and has common foot abnormalities such as flat feet, bunions, or ham
mertoes [11-14]

Nerve damage:

People with long-standing or poorly controlled diabetes are at risk for having damage to the nerves in their feet. The medical term for this is peripheral neuropathy. Because of the nerve damage the patient may be unable to feel their feet normally. Also, they may be unable to sense the position of their feet and toes while walking and balancing. With normal nerves, a person can usually sense if their shoes are rubbing on the feet or if one part of the foot is becoming strained while walking. A person with diabetes may not properly sense minor injuries (such as nuts, scrapes, blisters), signs of abnormal wear and tear (that turn into calluses and corns), and foot strain. Normally, people can feel if there is a stone in their shoe, then remove it immediately. A person who has diabetes may not be able to perceive a stone. Its constant rubbing can easily create a sore

Poor circulation:

Especially when poorly controlled, diabetes can lead to accelerated hardening of the arteries or atherosclerosis. When blood flow to injured tissues is poor, healing does not occur properly

Trauma to the foot:

Any trauma to the foot can increase the risk for a more serious problem to develop.

Infections: Athlete's foot of the fungal skin can lead to more serious bacterial infections. Ingrown toenails should be handled right away by a foot specialist. Toenail fungus should also be treated.

Smoking:

Smoking any form of tobacco causes damage to the small blood vessels in the feet and legs. This damage can disrupt the healing process and is a major for infections and amputations. The importance of smoking cessation cannot be overemphasized.

4. Symptoms of Diabetic Foot

Persistent pain can be a symptom of sprain, strain, bruise, overuse improperly fitting shoes, or underlying infection. Redness can be a sign of infection, especially when surrounding a wound or of abnormal rubbing of shoes or socks. Swelling of the feet or legs can be a sign of underlying inflammation or infection, improperly fitting shoes, or poor venous circulation. Other signs of poor circulation include the following: Pain in the legs or buttocks that increases with walking but improves with rest (claudication) Hair no longer growing on the lower legs and feet. Hard shiny skin on the legs. Localized warmth can be a sign of infection or inflammation, perhaps from wounds that won't heal or that hea the skin is serious and can result from abnormal wear and tear, injury, or infection. Calluses and corns may be a sign of chronic trauma to the foot. Toenail fungus, athlete's fo may lead to more serious

bacterial infections. Drainage of pus from a wound is usually a sign of infection. Persistent bloody drainage is also a sign of a potentially serious foot problem. A limp or difficulty walking can be sign of joint problems, serious infection, or improperly fitting shoes. Fever or chills in association with a wound on the foot can be a sign of a limb- threatening or life-threatening infection. Red streaking away from a wound or redness spreading out from a wound is sign of a progressively worsening infection. New or lasting numbness in the feet or legs can be a sign of nerve damage from diabetes, which increases a person's risk for leg and for Monofilament test: This test checks the ability of the foot to feel things touching it, like a feather or a pin[15].

Thermal sensation test: This test checks the ability to feel heat on the feet.

Arterial Doppler test:

An arterial Doppler test is done to check blood flow through an artery. A small metal disc with gel on it is placed on the skin over the artery. A whooshing sound is heard when the blood is flowing through the artery. By this the blood flow to the foot can be tested- whether it is adequate or inadequate.

5. Treatment of Diabetic Foot

The gold standard for diabetic foot ulcer treatment includes debridement of the wound, management of any infection [18] revascularization procedures when indicated, and off-loading of the ulcer. Other methods have also been suggested to be beneficial as add-on therapies, such as hyperbaric oxygen therapy, use of advanced wound care products, and negative-pressure wound therapy (NPWT) [19-22].Some other measures to treat diabetic foot include:

1. Polyurethane gel foot orthoses:

Polyurethane gel, when utilized in foot orthoses (special insoles), is more effective in reducing shear than foam materials. Studies have indicated that foot orthoses should be beneficial in improving the long-term prognosis in the diabetic foot [23].

2. Cadexomer - iodine gel:

Cadexomer - iodine gel is better known as lodoflex and lodosorb. This is a type of wound gel that clinicians use to treat heavily draining wounds or wounds that produce a large amount of liquid exudate due to bacteria, it is available in the market as sheet dressing, powder and ointment, It has the following advantages: [23]

a. Iodine is released slowly over a long period of time.
b. It is effective against all types of microbes.
c. It has low MIC value.

3. Silver dressings:

Silver dressings are used in wound healing in diabetic foot. The two most common ones are:

i) **Actisorb silver:**

It is an activated charcoal cloth impregnated with silver. It is reported to absorb bacteria, which are then inactivated by silver. It provides a silver coating over the wounds**.**

ii) **Acticoat:**

It consists of a rayon/polyester non woven core laminated between layers of silver- coated high density polyethylene mesh. It provides a silver coating over the wounds [24]

4. Leptospermin: It is a honey-based ointment that stimulates wound healing. Honey is used because of its following properties:

- It provides a hydrated healing environment.
- It rapidly clears bacteria from infected wounds.
- It creates a protective barrier to prevent cross-infection of wounds.
- It has an anti-inflammatory action resulting in reduced edema and improved blood flow, along with reduction in pain [23].

5. Linezolid:

Linezolid is an oxazolidinone antibiotic, which has been found to be effective in treating diabetic foot. Linezolid can treat a variety of infections including some caused by bacteria resistant to the drug methicillin. Methicillin resistant Staphylococcus aureus (MRSA) has become a major cause of infections, including diabetic foot. It can be given both orally and intravenously [23].

6. Debridement:

Debridement is carried out in all chronic wounds to remove surface debris and necrotic tissues. It improves healing by promoting the production of granulation tissue and can be achieved surgically, enzymatically, biologically, and through autolysis. Surgical debridement, known also as t performed by scalpels, and is rapid and effective in removing hyperkeratosis and dead tissue. Particular care is taken to protect healthy tissue, which has a red or deep pink (granulation tissue) appearance. Using a scalpel blade with the tip pointed at a 45^0 angle, all nonviable tissue must be removed until a healthy bleeding ulcer bed is produced with saucerization of the wound edges.Enzymatic debridement can be achieved using a variety of enzymatic agents, including crab-derived collagenase, collagen from krill, papain, a combination of streptokinase and streptodornase, and dextrans. These are able to remove necrotic tissue without damaging the healthy tissue. Although expensive, enzymatic debridement is indicated for ischemic ulcers because surgical debridement is extremely painful in these cases. Biological debridement has been applied recently using sterile maggots. Maggots have the ability to digest surface debris, bacteria, and necrotic tissues only, leaving healthy tissue intact. Recent reports suggest that this method is also effective in the elimination of drug-resistant pathogens, such as methicillin resistant Staphylococcus aureus, from wound surfaces. Autolytic debridement involves the use of dressings that create a moist wound environment so that host defense mechanisms (neutrophils, macrophages) can clear devitalized tissue using the body's cytokines,enzymes platelets,.white Autolysis blood cells, growth is enhanced by the use of proper dressings, such as hydrocolloids, hydrogels, and films. Autolysis is highly selective, avoiding damage to the surrounding skin [25-27].

7. Off-loading:

Off-loading of the ulcer area is extremely important for the healing of plantar ulcers. Any existing foot deformities may increase the possibility of ulceration, especially in the presence of diabetic peripheral neuropathy and inadequate off-loading. The most effective method of off-loading,

which is also considered to be the gold standard, is the non-removable total contact cast (TCC). It is made of plaster or fast-setting fiberglass cast materials, has relatively low costs, and permits restricted activity. Non-removable TCCs are indicated for the selective off- loading of ulcers located at the forefoot or mid foot. Severe foot ischemia, a deep abscess, osteomyelitis, and poor skin quality are absolute contraindications to the use of a non-removable TCC. Non-removable TCCs work by distributing the plantar pressures from the forefoot and mid foot to the heel. They allow complete rest of the foot whilst also permitting restricted activity. Non-removable TCCs also reduce edema, and compliance with treatment is necessarily high [30]. There are a number of removable cast walkers (RCW), which usually have a lightweight, semi rigid shell that helps support the limb whilst also providing full-cell protection. The sole is of a rocker type, offering off-loading of the forefoot during standing and walking.

The foot base is wide and there is enough room for dressings. In some RCWs, overlapping air cells provide intermittent pneumatic compression for edema reduction. In other RCWs, there are additional layers of foam or other soft material, offering total contact. A modification of RCWs is an instant total-contact cast (ITCC), where there is a wrapping layer of cohesive tape or plaster bandage around the RCW. The aim of the ITCC is to combine the efficacy of a TCC with the easy application of a RCW. Half shoes are another solution for patients who cannot tolerate other methods of off-loading, although they provide less pressure relief than a cast boot and are difficult to walk in. Therapeutic shoes, custom insoles, and the use of felted foam are alternative methods to off- load wounds located on the forefoot, and can reduce pressure at the site of ulceration by 4-50% [28-29].

8. Dressings:

Ulcers heal more quickly and are often less complicated by infection when in a moist environment. The only exception is dry gangrene, where the necrotic area should be kept dry in order to avoid infection and conversion to wet gangrene. Moreover, it has been reported that local concentrations of growth factors [platelet-derived growth factor-beta (PDGF-beta), transforming growth factor-beta] are low in patients with chronic ulcers. The ideal dressing should be free from contaminants, be able to remove excess exudates and toxic components, maintain a moist environment at the wound-dressing interface, be impermeable to microorganisms, allow gaseous exchange, and, finally, should be easily removed and cost-effective. Various dressings are available that are intended to prevent infection and enhance wound healing, and several studies support their effectiveness for this purpose [31-33].

9. Growth factors:

PDGF- beta (becaplermin) has been developed as a topical therapy for the treatment of non-infected diabetic foot ulcers. It is applied in the form of a once-daily gel along with debridement on a weekly basis. Becaplermin gel is a platelet-derived growth factor (PDGF) of recombinant human origin. PDGF stimulates and recruits macrophages, neutrophils and fibroblasts, stimulates angiogenesis; stimulates granulation tissue formation, wound contraction, and wound remodeling. Becaplermin gel should be used in wounds that have adequate blood supply and a clean wound bed (one without infection or necrosis). When used in conjunction with appropriate wound care, becaplermin gel has been shown to increase the incidence of complete wound closure and decrease the time to complete wound closure [34-36].

The amount of becaplermin gel applied varies by wound size . The amount should be measured out (into a clean surface and the gel applied using an application aid to a thickness of1/16 inch. The gel should be covered with a saline moistened gauze pad and left in place for 12 hours. After 12 hours, remove the gauze, rinse the ulcer with saline, and apply a new moistened dressing (without becaplermin gel) for the remaining 12 hours. Repeat this application process once daily. Platelet-rich plasma (PRP) is an autologous product, extracted from the includes a high platelet concentration in a fibrin clot that can be easily applied to the ulcer area clot is absorbed during wound healing within days to weeks following its application. The results of the subcutaneous administration of granulocyte colony-stimulating factor (GCFS) in patients with infected foot ulcers vary, with some studies indicating faster resolution of the infection and faster healing. Basic fibroblast growth factor (BFGF) is known to be beneficial in the formation of granulation tissue and normal healing. Epidermal growth factor (EGF) acts on epithelial cells, fibroblasts, and smooth muscle cells to promote healing.[37-41]

10. Bioengineered Skin Substitutes

Tissue-engineered skin substitutes are classified into allogenic cell—containing autologous cell-containing and a cellular matrices. The first two types of matrix contain living cells, such as keratinocytes or fibroblasts, in a matrix, while a cellular matrix are free of cells and act by releasing growth factors to stimulate revascularization and wound healing. Evidence shows that bioengineered skin substitutes may be a promising therapeutic adjunct therapy to the standard wound care for the management of non-infected diabetic foot ulcers.

11. Extracellular Matrix Proteins [45]: Hyaff is a semi synthetic ester of hyaluronic acid which facilitates the growth and movement of fibroblasts, and controls hydration. Other available products contain lyophilized collagen from various sources (bovine, porcine), alone or in combination with alginates, cellulose or antibiotics. Collagen seems to induce the production of endogenous collagen and to promote platelet adhesion and aggregation. It has been reported to be safe and effective as an adjunctive therapy in the management of foot ulceration.

12. MMP Modulator [46-48]:

Matrix metallo proteinases regulate the extracellular matrix components. During normal wound healing, there is a balance between the construction and the destruction of the extracellular matrix. In chronic wounds, a high expression of MMP-2 in fibroblasts and the endothelium is detected

and is believed to favor destruction. Thus, down regulation of MMP-2 expression may enhance the healing process. DerMax is a dressing containing metal ions and citric acid, and its topical application is associated with a lower expression of MMP-2 by fibroblasts and endothelial cells. Metal ions inhibit the production of reactive oxygen species by polymorpho nuclear cells, and citric acid acts as a scavenger of superoxide anions.

13. Negative-Pressure Wound Therapy [49-50]:

Negative-pressure wound therapy (NPWT) has emerged as a new treatment for diabetic foot ulcer. It involves the use of intermittent or continuous sub-atmospheric pressure through a special pump (vacuum-assisted closure) connected to a resilient open-celled foam surface dressing covered with an adhesive drape to maintain a closed environment. The pump is connected to a canister to collect wound discharge and exudates. NPWT optimizes blood flow, decreases tissue edema and removes exudates, proinflammatory cvtokines and bacteria from the wound area. It is performed after debridement and continued until the formation of healthy granulation tissue at the surface of the ulcer. Currently NPWT is indicated for complex diabetic foot wounds; however, it is contraindicated for patients with an active bleeding ulcer.

14. Hyperbaric Oxygen [51-53]:

There is strong evidence that fibroblasts, endothelial cells, and keratinocytes are replicated at higher rates in an oxygen-rich environment. Moreover, leukocytes kill bacteria more effectively when supplied by oxygen. Adverse effects include barotraumas to the ears and sinuses. pneumothorax, transient changes in visual acuity, and seizures.

15. Living skin equivalent (LSE) products [54]:

Living skin equivalent (LSE) products are the newest technological advances for diabetic foot ulcers. One LSE product consists of dermal fibroblasts cultured in vitro onto a bio-absorbable mesh to produce a metabolically active tissue that has histological characteristics similar to the dermal papillary of newborn skin. Another available LSE product resembles living human skin in that it consists of two primary layers: an epidermis and a dermis. The well-differentiated epidermal layer includes a protective stratum corneum formed from human living keratinocytes The dermal layer is composed of living human fibroblasts dispersed in a bovine collagen matrix. The keratinocytes and fibroblasts are cultivated from human infant foreskin. The skin equivalent used is a bilayered, living human skin analog that consists of both a dermal and epidermal layer The dermis is made from human cultured fibroblasts(from donated neonatal foreskin) and purified bovine collagen. The epidermis consists of keratinocytes that are also derived from the neonatal foreskin. Compared to normal skin, the skin equivalent is devoid of major immunogenic components, resulting in a lack of immunological response and rejection reaction when applied in human wounds. Application of the skin equivalent stimulate healing through the action of cytokines and other matrix components that stimulate epithelialization from the edge of the wound and promote the formation of new skin at the applied area, resulting in frank graft which leads to a draft integration similar to the one observed autologous skin grafting.

Amino Acids help diabetic foot wounds [55-56]:

Researchers at University of Nevada School of Medicine in Las Vegas, Nevada find supplementation with certain amino acids can helpdiabetic foot wounds. Targeted amino acid supplementation with arginine, glutamine, and beta-hydroxyl-beta methyl butyrate (HMB) is effective at helping diabetic foot wounds. Arginine, glutamine and beta-hydroxyl-beta methyl butyrate (HMB) help diabetic foot wounds by increasing the production of hydroproline, which is needed for the making of collagen, the protein needed for treating diabetic foot ulcers. Amino acid supplementation significantly improves wound depth.

6. Conclusion

Prevention of diabetic foot ulceration is critical in order to reduce the associated high morbidity and mortality rates, and the danger of amputation. It is essential to identify the *"foot at* through *risk,"* careful inspection and physical examination of the foot followed by neuropathy and vascular tests.

7. References

[1] Abbott CA, Carrington AL, Ashe 11, North-West Diabetes Foot Care Study et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetes Med. 2002; 19:377-384.

[2] Boulton AJ. The diabetic foot-an update. Foot Ankle Surg. 2008; 14:120-124.

[3] Centers for Disease Control and Prevention Lower extremity disease among persons aged 40 years with and without diabetes—United States, 1999-2002. MMWR Morb Mortal Wkly Rep. 2005;54: 1158- 1160.

[4] Lauterbach S. Kostev K, Kohlmann T. Prevalence of diabetic foot syndrome and its risk factors in the UK. J Wound Care. 2010; 19:333-337.

[5] Prompers L, Huijberts M, Schaper N, et al. Resource utilization and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia. 2008;51: 1826—1834.

[6] Kumar S, Ashe HA, Parnell LN, et al. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. Diabet Med. 1994;11:480-484.

[7] Tesfaye S, Stevens LK, Stephenson JM, et al. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia. 1996;39: 1377-1384.

[8] Frykberg RG, Lavery LA, Pham H, Harvey C, Harklcss L, Veves A. Role of neuropathy and high foot pressures in diabetic foot ulceration. Diabetes Care. 1998;21:1714-1719.

[9] Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations—a review of global variability in incidence. Diabetes Med. 2011; 28:

1144-1153.

[10] Bowering CK. Diabetic foot ulcers. Pathophysiology, assessment, and therapy. Can Fam Physician. 2001 ;47:1007-1016.

[11] Hoffman AF. Evaluation of arterial blood flow in the lower extremity. Clin Podiatr Med Surg. 1992; 9: 19-56.

[12] Katsilambros N, Dounis E, Makrilakis K, Tentolouris N, Tsapogas P. Atlas of the diabetic foot. 2. Oxford: Wiley-Blackwell: 2010.

[13] Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med. 1998;158:157-162.

[14] Doupis J, Veves A. Classification, diagnosis, and treatment of diabetic foot ulcers. Wounds. 2008; 20: 117- 126.

[15] Pham H, Armstrong DG, Harvey C, Harkless LB. Giurini .JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care. 2000; 2(3):606-611.

[16] Kravitz SR. McGuire J, Shanahan SD. Physical assessment of the diabetic foot. Adv Skin Wound Care. 2003; 16:68-75.

[17] Boulton AJ, Armstrong DG, Albert SF, American Diabetes Association: American Association of Clinical endocrinologists et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care. 2008; 31:1679-1685.

[18] Hinchliffe RJ, Valk GD, Apelqvist J. et al. Specific guidelines on wound and wound-bed management. Diabetes Metab Res Rev. 2008; 24(1): S18-S189.

[19] Brem H, Sheehan P. Boulton J. Protocol for treatment of diabetic foot ulcers. Am 1 Surg. 2004; 87: 1S- 10S.

[20] Game FL, Hinchliffe RJ, Apelqist J. et al. A systematic review of intentions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Re. 2012;28 (1): 119- 141.

[21] Pound N, Chipchase S, Treece K, Game F, Jeffcoate W. Ulcer-free survival following management of foot ulcers in diabetes. Diabetic Med. 2005; 22: 1306-1309.

[22] Clark RAF. Wound repair: overview and general considerations. In: Clark RAF, editor. The molecular and cellular basis of wound repair. New York: Plenum Press. 1996: p. 3-50.

[23] Gupta RN, Pandey A, Ghosh S. Diabetic foot: Pathogenesis, management and recent advances Pharma Times, 2008; 40(8): 13-15.

[24] Tredget EE, Shankowskv HA, Groeneveld A, Burrell R. A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment burn wounds. J Burn Care Rehabil. 1998; 19:531-537.

[25] Lebrun E, Tomic-Canic M, Kirsner RS. The role of surgical debridement in healing of diabetic foot ulcers. Wound Repair Regen. 2010;18:433-438.

[26] Smith RG. Enzymatic debriding agents: an evaluation of the medical literature. Ostomv Wound Manage. 2008;54:16-34

[27] Saap LJ, Falanga V. Debridement performance index and its correlation complete closure of diabetic foot ulcers. Wound Repair Regen. 2002;10:354-359.

[28] Burns J, Begg L. Optimizing the offloading properties of the total contact cast for plantar foot ulceration. Diabetic Med. 2011;28:179-185.

[29] Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vase Surg. 2010; 52 (2.):37S-43S.

[30] Armstrong DG, Lavery LA, Wu S. Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care. 2005; 28:551-554.

[31] Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis. 2004; 39(2): S100-S103.

[32] Harding KG, Jones V. Price P. Topical treatment: which dressing to choose. Diabetes Metab Res Rev. 2000;16 (1):S47-S50.

[33] Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg. 2002; 137:822-827.

[34] Papanas N, Maltezos E. Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers. Drug Saf. 2010;33:455-461.

[35] Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. J Vasc Surg. 1995;21:71-8.

[36] Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double -blind study. Diabetes Care. 1998;21:822-827.

[37] Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst Rev. 2009; (8):CD006810.

[38] Huang P, Li S, Han M, Xiao Z, Yang R, Han ZC. Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes. Diabetes Care. 2005;28:2155-2160.

[39] Uchi H, Igarashi A, Urabe K, et al. Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. Eur J Dermatol. 2009;19:461-

468

[40] Tuyet HL, Nguyen Quh, Vo Hoang Minh H, et al. The efficacy and safety of epidemical growth factor in treatment of diabetic foot ulcers: the preliminary results. Int Wound J.2009;6:159-166.

[41] Tsang MW, Wong WK. Hung CS. et al. Human epidermal growth factor enhances healing of diabetic foot ulcer. Diabetes Care. 2003; 26: 1856-1861.

[42] Ehrenreich M, Ruszczak Z. Update on tissue-engineered biological dressings. Tissue Eng. 2006; 12:2407- 2424.

[43] Uccioli L, Giurato L, Ruotolo V, et al. Two-step antilogous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. Int J Low Extreme Wounds. 2011;10:80-85.

[44] Moustafa M, Simpson C, Glover M, et al. A new antilogous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. Diabetic Med. 2004; 21:786-789.

[45] Niezgoda JA, Gus CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. Adv Skin Wound Care. 2005; 18:258-266.

[46] Karim RB, Brito BL, Dutrieux RP, Lassance FP, Hage JJ. MMP-2 assessment as an indicator of wound healing: a feasibility study. Adv Skin Wound Care. 2006; 19:324-327.

[47] Pirayesh A, Dessy LA, Rogge FJ, et al. The efficacy of a polyhydrated ionone impregnated dressing in the treatment of recalcitrant diabetic foot ulcers: a multi-centre pilot study. Acta Chit Belg. 2007; 107:675-681.

[48] McCallon SK, Knight CA, Valiulus JP. Cunningham MW, McCulloeh JM, Farinas LF. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds Ostomy Wound Manage. 2000; 46(34): 28-32.

[49] Xie X, McGregor M, Dendukuri N. The clinical effectiveness of negative pressure wound therapy: a systematic review. J Wound Care. 2010:19:490-495.

[50] Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. Ann Vasc Surg. 2003; 17: 645-649.

[51] Broussard CL. Hyperbaric oxygenation and wound healing. J Vast Nurs. 2004;22:42-48.

[52] Kessler L, Bilbault P. Ortga F. et al. Hyperbaric oxygenation accelerates the healing rate of non-ischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care. 2003; 26:2378-2382.

[53] Tiaka EK, Papanas N, Manolakis AC, Maltezos E. The role of hyperbaric oxygen in the treatment of diabetic foot ulcers. Angiology: 2011.

[54] Mansbridge J. Skin substitutes to enhance wound healing. Expert Opinion Investigation Drugs. 1998;7:803-809.

[55] Edmonds M, Bates M, Doxford M, Gough A, Foster A. New treatments in ulcer healing and wound infection. Diabetes Metab Res Rev. 2000; 16 (1):S51-S54.

[56] Jones MA, Rivera M, Puccinelli CL, Wang MY et al. Targeted Amino Acid Supplementation in diabetic foot wounds. Pilot Data and a review of the Literature. Surg. Infect. 2014: Sept. 12.

[57] Larsson J, Apelqvist J. Agardh CD, Stenström A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabet Med. 1995;12:770-776.

[58] Lavery LA, Wunderlich RP, Tredwell JL. Disease management for the diabetic foot: effectiveness of a diabetic foot prevention program to reduce amputations and hospitalizations. Diabetes Res Clin Pract. 2005; 70:31-37.